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REMARKS

Claims 9-14 and 18-20 are pending and under rejection in the application. No amendments have been made herein. Reconsideration of the application is hereby respectfully requested.

I. Rejection of claims 9-14, 19-21 under 35 USC 103 IVO Schwartz US 4886741

The Examiner has rejected claims 9-14 and 19-21 under 35 USC 103(a) as being obvious in view of the disclosure of US 4886741 (Schwartz). Applicants respectfully traverse this basis of rejection for the following reasons.

Claim 9 is the sole independent claim and is directed to a method of automatically hybridizing a polynucleotide probe composition to at least one target on a solid substrate, the method being executed in an automated staining system having evaporation inhibitor liquid covering a polynucleotide hybridization buffer-covered target on the slide, the improvement comprising the step of automatically hybridizing the target with the polynucleotide probe composition in the presence of low molecular weight dextran sulfate having a molecular weight range from about 8,000 to about 16,000 daltons, wherein the polynucleotide probe composition contains at least one sequence complementary to a coding region of the target.

US Patent No. 4,886,741 (Schwartz) describes the use of dextran sulfate for use as a volume exclusion agent for *in situ* hybridization of short (<50 bases) oligonucleotide probes to their target polynucleotides. The Examiner contends that the '741 patent teaches using volume exclusion agents such as dextran sulfate, and that its preferred polymer weight is at least 10,000 daltons. However, the '741 patent does not specifically describe what weight of dextran sulfate was used in the experiments. The '741 patent states that "The preferred polymer weight is at least 10,000 daltons, and no more than 2,000,000 daltons . . ." Col. 4, lines 14-15. The '741 patent discloses the broad range of 10,000 to 2,000,000, but has no specific teaching that low molecular weight dextran sulfate has any actual utility as a volume exclusion agent. In fact, the '741 patent discloses that the most preferred molecular weight range is 400,000 to 600,000 daltons. Applicants point out that the reference merely teaches that dextran sulfate exists over the

range of 10,000 to 2,000,000 and may be useful as a volume exclusion agent over the same range.

Applicants contend that they have selected an operating range (8,000 to 16,000 daltons) from within the broad range of molecular weights suggested by Schwartz, and shown the claimed range to have the unanticipated surprising result of being an effective volume exclusion agent, in the environment of an automated stainer. This is due to the lower viscosity of the low mol. wt. dextran sulfate, a fact unappreciated by the prior art in the context of in situ hybridization. Applicants selected a low molecular weight range of dextran sulfate which is surprisingly advantageous given the prior art teaches away from the use of dextran sulfate due to its high viscosity at high concentrations. For instance, it was recognized by Brigatti in US 5,116,727 that increasing concentrations of dextran sulfate should be avoided in capillary gap environments due to the increased viscosity associated with it:

> Unfortunately many volume exclusion polymers such as dextran sulfate cause increasing viscosities and surface tensions at increasing concentrations. This increased viscosity inhibits the probe from entering and exiting from small narrow spaces such as microcentrifuge tubes, pipette tips and plastic conduction lines as employed in various analyzers and such as capillary action gaps.

'727 patent, col. 1 line 67 – col. 2 line 6. Applicants' environment is very similar to a capillary gap environment due to the small (300 ul) available volume for reaction.

The Examiner admits that Schwartz does not disclose the use of low mol. wt. dextran sulfate in an automated environment similar to Ventana's staining systems. However, the Examiner then cites *In re Venner* for the proposition that "broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art." MPEP 2144.04 (III). Reliance on *Venner* is misplaced because Applicants claimed invention does not replace a manual activity with an automated one. Applicants are claiming an improved method of *in situ* hybridization in an automated tissue staining environment by automatically hybridizing a target with a polynucleotide probe composition in the presence of low molecular weight dextran sulfate having a molecular weight range from about 8,000 to about 16,000 daltons. The Examiner seems to be arguing under *Venner* that Applicants merely automated a manual method (which is obvious), while that is not the case. For *Venner* to

apply, the prior art would necessarily be a manual method of *in situ* hybridization using a low molecular weight dextran sulfate exclusion agent, which Applicants then merely automated. That is clearly not the case as no cited art has shown the use of dextran sulfate as a useful volume exclusion agent at this low weight. In sum, there was no manual method of ISH using low molecular weight dextran sulfate to be automated and so *Venner* does not apply.

In re Aller, 105 USPQ 233 is next cited by the Examiner as supporting a finding of obviousness of the optimum or workable ranges based on routine optimization where the general conditions of a claim are disclosed in the prior art. The general range disclosed by Schwartz is that of dextran sulfate existing over the molecular weight range of 10,000 to 2,000,000. Importantly, Schwartz does not teach which end of the range is useful for ISH in the specifically claimed microenvironment of Applicants' method. Taking the teachings of Schwartz, one of ordinary skill would have used the "most preferred" range, which was 400,000 to 600,000 daltons, and varied its concentration.

In *Becket v. Coe*, 69 App.D.C. 51, 98 F.2d 332, Becket had discovered and claimed an allegedly new deep-drawing stainless steel. The prior art references disclosed broad ranges which included the more restricted ranges of Becket's claimed alloy. However, the prior art references, which were foreign patents, in no way indicated that the patentees had sought or had found Becket's desirable discovery of a new deep-drawing stainless steel. The court was of the opinion that Becket's particular proportions in his restricted ranges were critical and resulted in a new and different metal of highly desirable properties. It concluded, in view of this, that Becket's claims were not anticipated by, and were patentable over, the cited prior art. Similarly, Applicant's discovery of the narrow range of useful mol. wts. of the claimed ISH method using dextran sulfate is surprising and hence patentable over the broad range disclosed by Schwartz.

Finally, Applicants rebut the Examiner's characterization that Schwartz disclose that "the preferred polymer weight is at least 10,000 daltons." The citation to column 3 is taken out of context. The complete citation is:

> The preferred polymer weight is at least 10,000 daltons, and no more than 2,000,000 daltons, with preferred weights being between 100,000 to 1,000,000, especially for the polyacrylate and polymethylacrylate polymers. The most preferred weight for the polymers is between 400,000 to 600,000 daltons.

Col. 3 lines 14-19.

For all of the reasons given above, Applicants assert that the claims are nonobvious over the disclosure of Schwartz, and respectfully request reconsideration of the application on that basis.

II. Rejection of claim 18 under 35 USC 103 IVO Schwartz, US 4886741 and Towne et al. US 6855552

The Examiner argues that the combination of the teachings of the method of Schwartz regarding dextran sulfate as an ISH exclusion agent, when combined with the automated tissue staining system having a tissue array of Towne et al. provide a *prime facie* case of obviousness of the ISH method applied to the probe array of claim 18. Applicants respectfully traverse this basis of rejection.

Claim 18 is directed to the method of claim 9 wherein the probe composition is arrayed on the solid substrate. The solid substrate is in a most preferred embodiment, a microscope slide. The probe is arrayed on the slide, which describes the arrangement of a DNA microarray, many of which are slide-based.

Towne et al. is directed to aqueous buffer compositions and methods for antigen retrieval in formalin-fixed, paraffin-embedded tissue, for automated methods for deparaffinizing tissue without the use of organic solvents, and automated methods for simultaneous deparaffinization and antigen retrieval. Contrary to the Examiner's statement that "This teaching suggests that after hybridization on a target, the probe composition is arrayed on a solid substrate" Towne et al. does **not** provide the element of having the probe composition arrayed on a solid substrate, although Towne et al. do disclose a tissue microarray. For that reason alone there is no *prima facie* case because the cited combination does not result in all of the claimed elements. Further, Applicants point out that the cited combination does not result in the claimed method because the claimed use of dextran sulfate (low molecular weight range of about 8,000 to about 16,000 daltons) is not suggested or taught to be a useful volume exclusion agent. Still further, the art does not teach or suggest using the low mol. wt. version in the constrained microenvironment of the LIQUID COVERSLIP as used and claimed by Applicants.

For the reasons cited above, Applicants assert that the Examiner has not made out a *prima facie* case of obviousness, and respectfully request reconsideration of the application on that basis.

III. Rejection of claim 18 under 35 USC 103 IVO Schwartz, US 4886741 and Richards et al. US 6296809

The Examiner has rejected claim 18 because "It would have been prima facie obvious to apply a probe composition arrayed on a solid substrate." Applicants respectfully traverse this basis of rejection.

Claim 18 is directed to the method of claim 9 wherein the probe composition is arrayed on the solid substrate. The solid substrate is in a most preferred embodiment, a microscope slide. The probe is arrayed on the slide, which commonly describes the arrangement of a DNA microarray, many of which are slide-based.

Richards et al. is directed to apparatus and methods for automatically staining or treating multiple tissue samples mounted on microscope slides. Individualized slide temperature control is accomplished by a heating system that has thermal platforms radially mounted to the carousel for heating the slides and sensing the temperature of each. The heating system also permits automated de-waxing and antigen retrieval. The apparatus of Richards et al. uses the LIQUID COVERSLIP™ design that is addressed in Applicants' claim 9 (col. 19 lines 44-53). DNA probes may be applied to the slides mounted on the stainer's carousel and hybridized to targets within the sample.

The Examiner has not made out a *prima facie* case of obviousness because the cited combination of elements does not result in Applicants' claimed invention. In the *Examination Guidelines for Determining Obviousness under 35 U.S.C. 103* (MPEP 2141) the Guidelines require that the Examiner, when making a rejection under section 103(a), first determine the facts under *Graham v. John Deere*, and then provide a reasoned basis for rejecting the claims as obvious. It is respectfully submitted that the Examiner has not done so here.

The Examiner rejected claim 18 on the basis of the combination of Richards et al. and Schwartz. Although the Examiner has not explained her reasoning with regard to Schwartz, Applicants assume that the previous basis applies. Therefore, Applicants

assume *arguendo* that the rejection is based on 1) Schwartz' teaching of a method of using dextran sulfate as a volume exclusion agent for short oligonucleotide probes, in combination with 2) Richards et al. teaching of a probe composition arrayed on a slide. The differences between the claimed subject matter of claim 18 and the combination of Schwartz and Richards et al. has not been clearly stated by the Examiner, however Applicants point out that the cited combination does not result in the claimed method because the claimed use of dextran sulfate (low molecular weight range of about 8,000 to about 16,000 daltons) is not suggested or taught to be a useful volume exclusion agent. Further, the art does not teach or suggest using the low mol. wt. version in the constrained microenvironment of the LIQUID COVERSLIP as used and claimed by Applicants.

For these reasons Applicants assert that the Examiner has not made out a *prima facie* case supporting the rejection, and therefore urge reconsideration of the application on that basis.

Respectfully submitted,

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